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# Accepted Manuscript

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**Results of Serial Myocardial Perfusion Imaging in End-Stage Renal Disease**

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**Abstract:** For patients awaiting renal transplantation, there is guideline consensus on the need for ischemia testing but no agreement on the frequency of repeat testing. Moreover, there are no data in this population evaluating changes in ischemia when assessed with serial myocardial perfusion imaging. Consecutive ESRD patients (n=649) were referred for cardiovascular risk stratification prior to renal transplantation between September 2007 and September 2013. Of these, 151 ( $54 \pm 9$  years, male 63%) underwent two stress-rest technetium-99<sup>m</sup> SPECT studies with CT attenuation correction in accordance with regional guidelines, which recommend repeat imaging in high-risk subjects who had not undergone renal transplantation within 3 years. An abnormal perfusion result was defined as a summed stress score  $\geq 4$ . The median interval between imaging was 39 months. At baseline, 28% of patients (42/151) had abnormal SPECT perfusion, half with a fixed defect. Nine subjects (6%) underwent revascularization between imaging studies after the baseline SPECT imaging demonstrated an ischemic perfusion defect size (PDS) affecting  $\geq 10\%$  of the myocardium. On repeat imaging, 60% (25/42) had abnormal perfusion. In the 72% (109/151) with normal baseline SPECT perfusion, 19% (21/109) demonstrated new ischemia at follow-up and 3% (3/109) had an ischemic PDS  $\geq 10\%$ . The development of new-onset ischemia was associated with systolic hypertension ( $p=0.015$ ), serum phosphate ( $p=0.043$ ) and Agatston score ( $p=0.002$ ) but not diabetes ( $p=0.12$ ). In conclusion, there is a high frequency of new-onset ischemia in ESRD patients awaiting renal transplantation. Further study is needed to define the optimal interval for repeat stress testing.

**Keywords:** End-stage renal disease; myocardial ischemia; SPECT MPI; renal transplant

## Introduction

Recent data confirm the prognostic utility of single-photon emission computed tomographic (SPECT) imaging in end-stage renal disease (ESRD),<sup>1,2</sup> although for patients awaiting renal transplantation there remains no guideline consensus on the need for repeat stress testing. The National Kidney Foundation recommend annual non-invasive stress testing for all patients with diabetes mellitus (DM), and repeating assessments every 24 months in “high-risk” non-diabetic patients.<sup>3</sup> In contrast, the American College of Cardiology Foundation emphasizes the lack of evidence that periodic screening of asymptomatic subjects awaiting renal transplantation is useful (Class IIb; Level C).<sup>4</sup> This discrepancy in position statements reflects a paucity of data informing the optimal surveillance strategy for subjects awaiting renal transplantation – to date, there are no studies that have evaluated serial changes in ischemia as defined by SPECT imaging. There is also lack of agreement on which non-invasive imaging modality for cardiovascular (CV) risk stratification is most appropriate in ESRD. Most transplant centers adopt an imaging strategy according to “best local expertise”, although many employ SPECT because of long-term data supporting its prognostic utility in ESRD.<sup>5,6</sup> One disadvantage of serial SPECT is cumulative exposure to radiation,<sup>7</sup> which merits a concerted effort to identify those patients likely to benefit from repeat testing thereby minimizing this long-term hazard. Thus, the aims of this study were to determine: 1) the proportion of subjects that develop myocardial perfusion defects while on the waiting list for renal transplantation and, 2) the clinical variables that predict new-onset myocardial ischemia.

## Methods

Consecutive patients with chronic kidney disease (CKD) stage 4 to 5D (n=649)

were referred to Queen Elizabeth Hospital Birmingham for CV risk stratification as part of a pre-transplant screening work-up from September 2007 to September 2013. In accordance with current guidelines compiled by a Joint Working Party of The British Transplantation Society and The Renal Association,<sup>8</sup> subjects underwent non-invasive CV risk assessment using technetium-99<sup>m</sup> SPECT studies with CT attenuation correction, if they fulfilled any of the following criteria: age >50 years, DM, suspected angina, or known ischemic heart disease. Subjects who had not undergone renal transplantation within 3 years (n=151) underwent repeat SPECT imaging in accordance with regional guidelines and were included in the present analysis (Figure 1). Formal ethical approval was not required because this study was a retrospective assessment of solely clinical data and was therefore regarded as a health outcomes evaluation. The conduct and reporting of this study was guided by the Strengthening the Reporting of Observational Studies in Epidemiology statement.<sup>9</sup>

Demographic and anthropometric data were collected on all patients through review of patient electronic records. In addition, a standard pre-scan assessment involving a detailed patient interview was performed to obtain information on symptoms, CV risk factors, previous CV events, and medication. A Duke pretest probability of coronary artery disease (CAD) was calculated at the time of the imaging study.<sup>10</sup> Routine hematology and biochemistry indices were also recorded. Diabetes mellitus was defined as a fasting glucose >126 mg/dl, history of DM, diabetic nephropathy, or currently receiving hypoglycemic treatment. Hypertension was defined as an office blood pressure >140/90 mmHg or currently taking anti-hypertensive medication. Hypercholesterolemia was defined as a serum cholesterol of >193 mg/dl or currently taking lipid reduction therapy. A history of CV disease was defined as having any of the following: CAD (myocardial infarction (MI), previous percutaneous, or surgical revascularization), heart failure, stroke, and peripheral vascular disease. Significant family history of CV disease

was defined as a first degree relative with a history of MI or ischemic stroke in men younger than 55 years and in women younger than 65 years.

The protocol for performing SPECT myocardial perfusion scintigraphy has been published.<sup>1</sup> Briefly, patients were asked to discontinue beta-blockers, rate-limiting calcium channel blockers, and caffeine products 24 hours before testing, and nitrate compounds were discontinued >6 hours before testing. All participants underwent 2-day stress-rest technetium-99<sup>m</sup> SPECT imaging with exercise treadmill or standard adenosine stress (140 mg/kg/min for 6 minutes) in those unable to achieve 85% maximal heart rate; and multi-slice coronary artery calcium scoring (CACS) was performed as routine. CT-based attenuation correction was performed during reconstruction of the SPECT data (Symbia T16, Siemens, Erlangen, Germany).

SPECT myocardial perfusion images were visually analyzed by 2 experienced observers (R.P.S. and B.H.) blinded to the baseline study (Quantitative Perfusion SPECT; Hermes Medical Solutions, Stockholm, Sweden). In addition to examination of raw images in cine mode, both non-attenuated and attenuated images were reviewed, and a report produced consistent with recommendations outlined in the American Society of Nuclear Cardiology Imaging Guidelines for Nuclear Cardiology Procedures.<sup>11</sup> Short-axis and vertical long-axis tomograms were divided into 17 segments for each study,<sup>11</sup> and segmental tracer uptake was evaluated using a validated semi-quantitative 5-point scoring system (0, normal; 1, equivocal; 2, moderate; 3, severe reduction of radioisotope uptake; and 4, absence of detectable tracer uptake).<sup>12</sup> The summed stress and rest scores were obtained by adding the scores of the 17 segments of the respective images. The sum of the differences between each of the 17 segments from these images was defined as the summed difference score, representing the amount of ischemia. These indexes were converted to the percentage of total myocardium involved with stress, ischemic, or fixed defects by dividing the summed scores by 68 (the maximum potential score = 4 × 17) and

multiplying by 100. The presence of abnormal perfusion was defined as a summed stress score of 4 or greater.<sup>13</sup> A stress-induced total perfusion defect size (PDS)  $\geq 15\%$  or an ischemic PDS  $\geq 10\%$  defined high risk for cardiac events.<sup>14</sup> Cardiac volumes and left ventricular (LV) ejection fraction were also calculated from the gated SPECT images.

CACS was calculated according to Agatston *et al.*<sup>15</sup> by the same two independent observers. Lesions were manually traced on CT images before semiautomatic quantification-derived vessel-specific scores were summated to yield the total CACS (syngo.via; Leonardo; Siemens Medical Solutions, Forchheim, Germany). Minimal, mild, moderate, and severe coronary calcification were defined as Agatston scores of 0 to 10 U, 11 to 100 U, 101 to 400 U, and  $>400$  U, respectively.<sup>14</sup>

The primary outcome of interest was the development of a new perfusion defect between imaging studies. All statistical analyses were performed with SPSS (version 21, IBM, Armonk, New York, USA). Data are expressed as mean  $\pm$  SD, median (interquartile range), or frequency (%), unless otherwise stated. The normality of distribution for continuous variables was determined using normality plots and the Kolmogorov-Smirnov test. Clinical characteristics of subjects with a normal baseline study were examined according to their follow up SPECT result. Continuous data were compared using independent t tests. Categorical data were compared using a chi-squared analysis or Fisher's exact tests where appropriate. Independent predictors of the development of a new perfusion defect were determined using multivariable logistic regression. A 2-tailed  $P < 0.05$  was considered statistically significant.

## Results

In total, 151 patients (CKD stage 4 to 5D) with serial SPECT/CT studies performed between January 2007 and June 2016 were identified (Figure 1). The baseline



characteristics of the study cohort are presented in Table 1. The mean age was 54 years, 63% were male, 39% had DM and 86% had a history of hypertension. The median interval between imaging was 39 months (IQR, 30-53 months). Over two-thirds (69%) of the cohort had at least mild CACS, and more than a third (35%) had severe CACS (Figure 2).

The distribution of myocardial ischemia at baseline and follow up SPECT studies is illustrated in Figure 3. At baseline, 28% patients (42/151) had abnormal SPECT perfusion, half with a fixed defect. Nine subjects (6%) underwent revascularization in the interval between imaging studies, after the baseline SPECT imaging demonstrated an ischemic PDS affecting  $\geq 10\%$  of the myocardium. On repeat imaging, 60% (25/42) still had abnormal perfusion, indicating that smaller perfusion defects affecting  $< 10\%$  of the myocardium had resolved in 41% (17/42). In 63% (29/46) of the patients with abnormal perfusion at follow up, there was an increase in PDS  $> 5\%$ ; the mean change in PDS in those subjects was 7%. Ten subjects (10/151, 7%) developed new fixed perfusion defects (mean PDS 8%), which was associated with a mean reduction in LVEF from 56 to 43%.

In the 72% (109/151) with a normal baseline SPECT study, 19% (21/109) demonstrated new-onset ischemia at follow-up, of which 3% (3/109) had an ischemic PDS  $\geq 10\%$ . Six percent of subjects with a normal baseline perfusion study (6/109) were re-classified as “high risk” after developing an ischemic PDS  $\geq 10\%$  and / or a total PDS  $\geq 15\%$ . Table 2 demonstrates the baseline clinical variables associated with the development of new-onset ischemia; these included the presence of chest pain ( $p=0.048$ ), an elevated systolic blood pressure ( $p=0.015$ ), increased serum phosphate ( $p=0.043$ ) and greater extent of coronary calcification ( $p=0.002$ ). There was an independent association between CACS and the development of a new perfusion defect that remained significant after adjustment for age, sex, systolic blood pressure, serum phosphate and presence of chest pain ( $\beta=0.39$ ,  $R^2=0.5$ ,  $p<0.001$ ). Although the mean CACS was higher in those

subjects that developed new-onset ischemia, there was no threshold CACS observed for this effect (Figure 4). More than half the subjects with new-onset ischemia had DM (51%) although this result did not reach statistical significance ( $p=0.12$ ). There was no difference in the rates of development of new-onset ischemia between different ethnic groups.

## Discussion

This study has demonstrated that almost 20% of ESRD patients awaiting renal transplantation develop new-onset myocardial ischemia over a median 3-year interval. Risk factors for the development of ischemia included the presence of chest pain, systolic hypertension, increased serum phosphate and greater extent of CACS. Relatively few subjects (6%) however, developed either an ischemic PDS  $\geq 10\%$  or stress-induced total perfusion defect size (PDS)  $\geq 15\%$  over this time-frame sufficient to warrant invasive investigation or intervention in the absence of symptoms. Of concern however, a similar proportion (7%) developed new fixed perfusion defects, which were associated with a mean fall in LVEF of 13%.

Our data are the first to provide insight into the proportion of subjects with ESRD that develop perfusion defects while on the waiting list for renal transplantation. To our knowledge, there are only three other studies that have focused on progression of ischemia as determined by SPECT.<sup>16-18</sup> Two of these were performed in asymptomatic patients with DM and akin to our study, approximately 1 in 5 developed abnormal perfusion during follow-up ranging from 2-3 years.<sup>16,17</sup> In the Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study, 358 of the initial 522 patients recruited underwent a second SPECT study to evaluate the change in myocardial perfusion at 3 years.<sup>16</sup> In this group, 20% had abnormal baseline perfusion in whom a large proportion (79%) then normalized. Comparable results were obtained in a study of 100

asymptomatic subjects with type 2 DM, normal resting ECG and no previous history of CV disease.<sup>17</sup> Again, 20% had abnormal baseline perfusion and a similar percentage (65%) then normalized over a shorter period of 2-year follow-up. The assumption made in both these studies was that regression of ischaemia was due to improved medical therapy, although in the latter, no relationship was found with the addition of anti-anginal medication. It is interesting to note that the rate of new-onset ischemia was similar across all studies although regression of ischemia was less common in our current ESRD cohort. Although no data regarding change in pharmacotherapy or medical management was recorded in our study, this lower rate of regression in ischemia may reflect the lack of efficacy of standard secondary prevention medication for CV disease in ESRD.<sup>19,20</sup>

It is well established that serial myocardial perfusion imaging with SPECT provides important information for managing patients with changing clinical presentation or, as in our study, in anticipation of such changes.<sup>21</sup> A retrospective, longitudinal study of 698 patients who had serial SPECT for clinical indications within  $16 \pm 9$  months (incorporating 147 subjects with ESRD), identified a significant increase in hard cardiac events (death, MI, revascularization) in those with a new perfusion abnormality, increase in PDS  $>5\%$  or a fall in LVEF  $>5\%$ .<sup>18</sup> These data suggest that the changes detected in our study are clinically meaningful; the mean change in PDS in subjects with abnormal perfusion at follow up in our cohort was 7%, which supports the concept of repeat testing, although the optimal frequency cannot be deduced for this specific population. This is emphasised by the development of new fixed defects associated with a fall in LV function in almost 1 in 20 of our subjects. In our study, the variables associated with the development of new-onset of ischaemia included systolic hypertension, increased serum phosphate and higher CACS. Patients who developed new-onset ischemia had on average greater extent of coronary calcification. There was however, no clear CACS threshold below which patients were free from developing abnormal perfusion (Figure 4) with a

small but significant proportion of subjects with only minimal coronary calcification developed new-onset perfusion defects. In previous research, we identified that abnormal perfusion was a more powerful predictor of adverse events than elevated CACS in those listed for renal transplantation over a median follow up of 18 months,<sup>1</sup> although coronary calcification may have more prognostic significance over a longer period of follow-up.<sup>22</sup>

The findings of our study are limited by their derivation from a single center and the retrospective observational nature of the data. No data were collected on change in pharmacotherapy or medical management, which makes it difficult to compare differences in the rate of regression of ischaemia with other cohorts. While longitudinal studies such as ours have advantages over cross-sectional cohort studies, by default our study is at risk of informative censoring, whereby only those patients who survived or failed to undergo transplantation could be included in the analysis. Indeed, the selected population of patients for this study who did not proceed to transplant are likely at greater long-term cardiovascular risk than those who were successfully transplanted.<sup>23</sup> A further issue is that the variance of the response changes is not known; in other words, the variability in SPECT due to technical or biological factors, as well as the intrinsic variability of the technique. In this respect, this study has the advantage of being performed in the same centre with the same reporting staff and equipment, following standardized protocols. Further prospective studies in larger populations that include data on intervening management and hard endpoints are still required.<sup>4</sup>

In conclusion, there is a high frequency of new-onset ischemia in patients with ESRD awaiting renal transplantation, particularly in the presence of systolic hypertension and severe coronary calcification. These data support the need for repeat stress testing in this high-risk cohort.

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**Figure 1.** Study consort diagram.

**Figure 2.** Distribution of CACS across the overall cohort.

**Figure 3.** Pie charts of the distribution of myocardial ischemia on SPECT stratified according to baseline ischemia. Abnormal perfusion was defined as a summed stress score of  $\geq 4$ . Data are N (%). Blue represents normal SPECT perfusion; green represents abnormal SPECT perfusion.

**Figure 4.** Relationship of CACS with the development of new-onset ischemia.



**Table 1.** Baseline demographics and clinical characteristics for study cohort.Data are number (%), mean  $\pm$  SD or median [interquartile range].\*Defined as an office blood pressure of  $> 140/90$  mmHg or currently taking hypertensive medications†Defined as a fasting serum cholesterol of  $>193$  mg / dL

Variable	n=151
Age (years)	53.6 $\pm$ 9.4
Men	95 (63%)
White	80 (53%)
Asian	55 (36%)
Black	14 (9%)
Other ethnicity	2 (1%)
Body mass index (kg / m <sup>2</sup> )	28.0 $\pm$ 7.2
Diabetes mellitus	59 (39%)
Diabetes-related treatment	
Diet-control	4 (3%)
Oral hypoglycemic agent	17 (11%)
Insulin	38 (25%)
Hypertension*	131 (86%)
Hypercholesterolemia†	110 (73%)
Current smoker	31 (20%)
Family history of coronary artery disease	5 (3%)
Number of cardiac risk factors	2.4 $\pm$ 1.0
Previous myocardial infarction	11 (7%)
Previous percutaneous coronary intervention	13 (9%)
Previous coronary bypass surgery	9 (6%)
Previous renal transplant	21 (14%)
Renal replacement therapy	64 (42%)
Haemoglobin (g / L)	115.4 $\pm$ 15.6
Total cholesterol (mg / dL)	166 $\pm$ 43
Calcium (mg / dL)	9.00 $\pm$ 0.72
Phosphate (mg / dL)	4.30 $\pm$ 1.08
Parathyroid hormone (pmol / L) [IQR]	22.2 [11.9 – 45.5]
Estimated Glomerular Filtration Rate (ml / min / 1.73 m <sup>2</sup> )	13.4 $\pm$ 8.4
Uric acid (mg / dL)	7.63 $\pm$ 2.15
Medications	
Aspirin	73 (48%)
Thienopyridine	8 (5%)
Beta-blocker	53 (35%)
ACE inhibitor/angiotensin receptor blocker	87 (58%)
Calcium channel blocker	69 (46%)
Diuretic	65 (43%)
Statin	104 (69%)
Duke pre-test probability (%) [IQR]	5 (3-8)
Symptomatic chest pain	35 (23%)
Ability to perform exercise stress to $>85\%$ maximal heart rate	58 (38%)
Left ventricular ejection fraction (%) [IQR]	56 [50 – 64]
Abnormal SPECT result (summed stress score $\geq 4$ )	42 (28%)
Summed stress score	2.7 $\pm$ 5.3
Total Perfusion Defect Size (% myocardium)	3.3 $\pm$ 8.0
Ischemic Perfusion Defect Size (% myocardium)	1.7 $\pm$ 4.0
Total Perfusion Defect Size $\geq 15\%$	11 (7%)

Ischemic Perfusion Defect Size  $\geq 10\%$

9 (6%)

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**Table 2.** Baseline characteristics of subjects with a normal baseline SPECT study stratified according to their follow up perfusion result (n = 109).

Variable	Normal myocardial perfusion (n = 88)	Abnormal myocardial perfusion (n = 21)	p
Age (years)	52.9 ± 9.6	50.8 ± 10.6	0.37
Men	50 (57%)	12 (57%)	0.98
White	47 (53%)	9 (43%)	0.39
BMI (kg / m <sup>2</sup> )	28.0 ± 7.1	27.7 ± 4.9	0.83
Diabetes mellitus	30 (34%)	11 (52%)	0.12
Smoker	40 (45%)	8 (38%)	0.54
Hypertension	76 (86%)	17 (81%)	0.12
Hypercholesterolaemia	57 (65%)	11 (52%)	0.29
Systolic blood pressure (mmHg)	137 ± 23	152 ± 32	<b>0.015</b>
Symptomatic chest pain	13 (15%)	7 (33%)	<b>0.048</b>
Duke pre-test probability (%)	6.2 ± 6.1	6.4 ± 5.0	0.89
Previous renal transplant	12 (14%)	3 (14%)	0.78
Renal replacement therapy	39 (44%)	8 (38%)	0.65
Ability to perform exercise stress	31 (35%)	8 (38%)	0.81
Haemoglobin (g / L)	117 ± 15	114 ± 16	0.43
Calcium (mg / dL)	9.12 ± 0.76	9.00 ± 0.60	0.52
Phosphate (mg / dL)	3.84 ± 1.05	4.37 ± 1.05	<b>0.043</b>
Uric acid (mg / dL)	7.51 ± 2.20	7.65 ± 2.10	0.84
Coronary artery calcium score (U)	526 ± 61	1404 ± 375	<b>0.002</b>
Left ventricular ejection fraction (%)	58 ± 12	57 ± 12	0.73

Data are mean ± SD and N (%). Continuous data are compared using independent t tests. Categorical data are compared using a chi-squared analysis. Bold values have a significant p-value (<0.05).